



ISFTD²⁰²⁶
PHILADELPHIA

**15th International Conference on
Frontotemporal Dementias**

**October 8–11, 2026
Philadelphia, PA**

**ASPIRE-FTD in FTD with *GRN* Mutations Study Update:
A Phase 1/2 Study to Evaluate AVB-101
Presenter: Prof. Rik Vandenberghe, KU Leuven**



Disclosures

- **Prof. Rik Vandenberghe's** institution has clinical trial agreements (RV as site PI) with Alector, AviadoBio, Biogen, Bristol-Myers Squibb, Denali, Eli Lilly, Johnson & Johnson, Merck, Roche and UCB. RV's institution has consultancy agreements with AC Immune and Novartis (RV as Data Safety Monitoring Board or Data Monitoring Committee member), and with Roche, VectorY, and AviadoBio (RV as member of international advisory board).
- ASPIRE-FTD (NCT06064890) is sponsored and funded by **AviadoBio Ltd.**
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ASPIRE-FTD Study Update: A Phase 1/2 Study to Evaluate AVB-101 in FTD with *GRN* Mutations

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Presented by **Prof. Rik Vandenberghe** on behalf of the ASPIRE-FTD investigators

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Introduction

- Mutations of the granulin gene are one of the most frequent causes of autosomal dominant frontotemporal degeneration
- The clinical phenotype of frontotemporal degeneration due to *GRN* mutations (FTD-*GRN*) is heterogeneous, mainly with behavioral and dysexecutive changes, primary progressive aphasia, or corticobasal syndrome
- Mean age of disease onset in FTD-*GRN* is 61 years (SD 8.8 years); median survival estimate is 6.63 years (range 6.08-7.98) ^{1,2}
- No therapy is currently available for this devastating disease, posing a large unmet clinical need

1. Moore et al, Lancet Neurol 2020

2. Borroni et al Lancet Neurol 2026



Introduction

- Granulin mutations cause haploinsufficiency, with progranulin protein levels $\leq 50\%$ of normal
- Over the past years several clinical development programs have been initiated using small molecule,¹⁻² protein replacement,³ antibody,⁴ and gene therapy⁵⁻⁷ approaches in FTD-*GRN*
- Gene replacement therapy (progranulin supplementation) has been studied through different routes of administration
- Ideally the transgene needs to be expressed adequately, and secreted progranulin protein broadly distributed across cortical and subcortical grey matter

1. VES001: NCT06226064, NCT06705192 (Klem et al., Nat Commun. 2026.
2. FRM-0334: NCT02149160 (Ljubenkova et al., JAMA Netw Open. 2021;4(9):e2125584)
3. DNL593/TAK-594: NCT05262023 (Berger et al., AAIC 2023 abstract)
4. Latozinemab/AL001: NCT03636204, NCT03987295, NCT04374136 (Kurnellas et al., J Transl Med. 2023;21:387)
5. LY3884963/PR006: NCT04408625 (Sevigny et al., Nat Med. 2024;30:1406-1415)
6. PBFT02: NCT04747431 (Voss et al., AAIC 2025 abstract)
7. AVB-101: NCT06064890 (Huang et al., AAIC 2026 abstract)

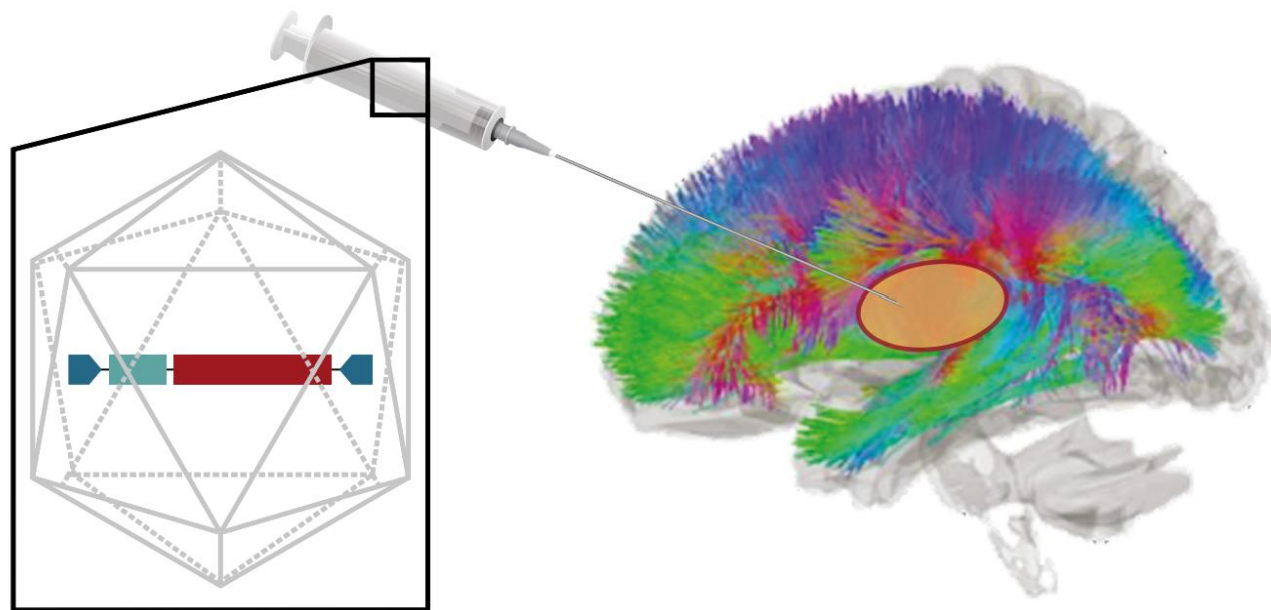


AVB-101 is an investigational gene therapy for the treatment of *FTD-GRN*

AVB-101



AVB-101 uses an **AAV9 vector** to deliver a functional copy of the *GRN* gene under control of a **neuronal-specific promoter**



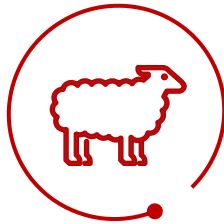
Targeted administration of relatively low doses of AVB-101 into the **thalamus** seeks to **exploit neuronal networks to maximise biodistribution** of the secreted PGRN protein throughout the brain



Preclinical studies demonstrated potency, precision & safety of ITM delivery



Suppressed neuronal lipofuscinosis and reactive microglia in *Grn*^{-/-} mice

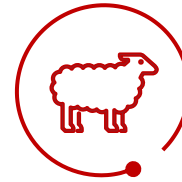


58 sheep/NHP underwent ITM delivery

Well tolerated, minimal systemic exposure

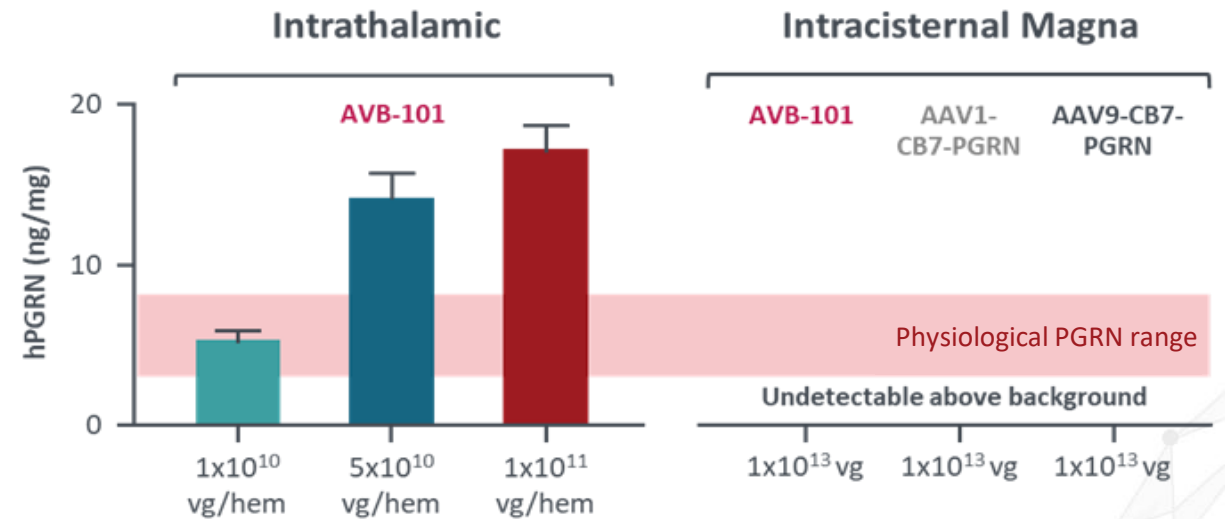


Widespread cortical/subcortical PGRN distribution



ITM delivery resulted in dose-dependent increase in progranulin (prefrontal cortex)

ICM did not increase cortical progranulin

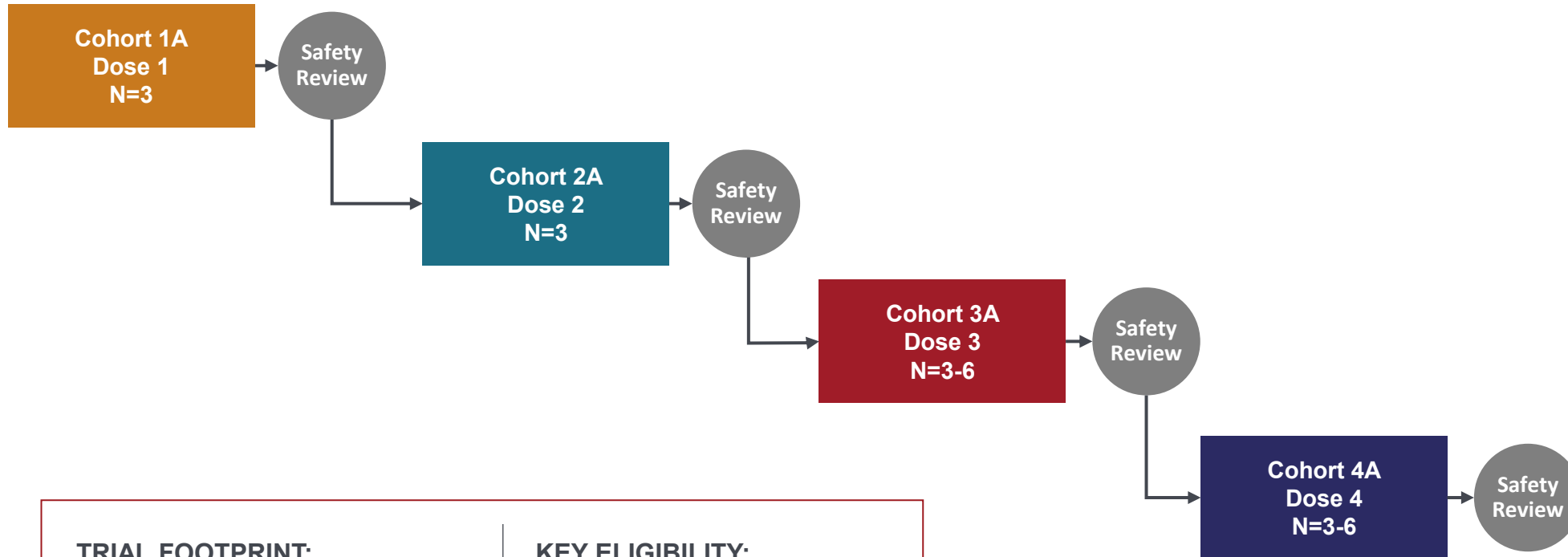


N=2 per dose group plus vehicle controls (not shown)

ITM = intrathalamic; ICM = intracisterna magna



ASPIRE-FTD open-label Phase I/II Trial is exploring the safety and efficacy of ascending doses of AVB-101



TRIAL FOOTPRINT:

- Open in 9 countries
US, UK, CA, PL, SP, NL, IT, BE, SE
- FHD March 2024
- Three cohorts completed
- **Currently recruiting into Cohort 4A**

KEY ELIGIBILITY:

- FTD diagnosis
(behavioural variant or PPA)
- Disease-causing GRN mutation
- Age 30-75 years
- CDR 0.5 to 2

SAFETY ASSESSMENTS

- Adverse Events
- Antibody Response
- Clinical Laboratories,
Physical/Neuro Exam
- Structural MRI

BIOMARKER ASSESSMENTS

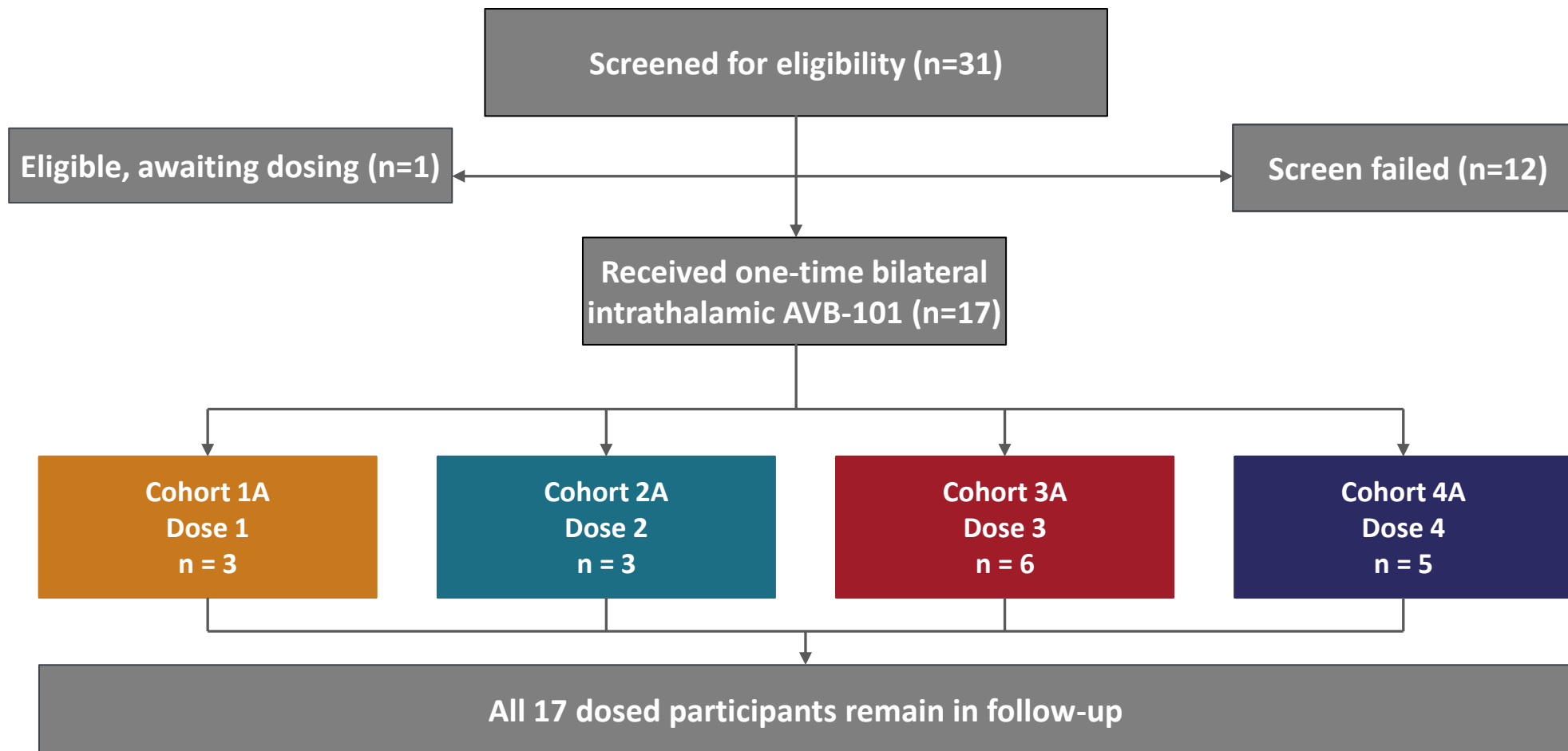
- CSF and serum PGRN levels
- Neurodegeneration (NfL) and
neuroinflammation (GFAP)
- Exploratory biomarkers
- Volumetric MRI

EXPLORATORY EFFICACY ASSESSMENTS

- CDR plus NACC-FTLD Global
Score, Sum of Boxes
- Cognitive/behavior
assessments (e.g. GENFI-Cog)
- Clinician/patient/caregiver
reported outcomes



Participant disposition



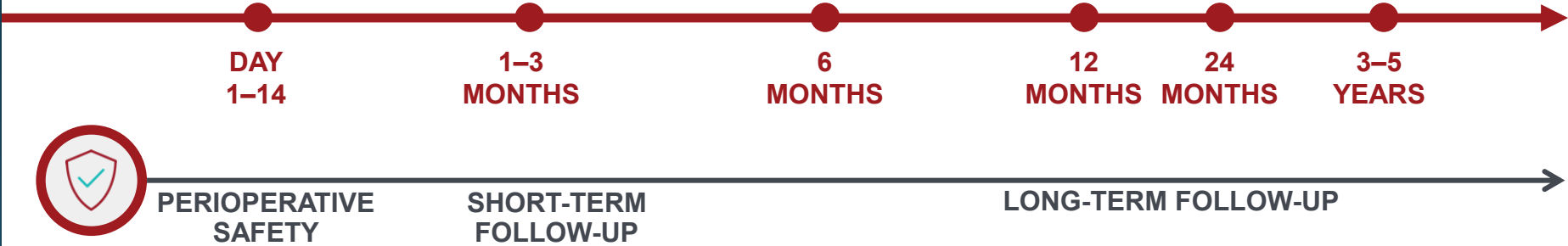
Data cut-off 30-SEP-2026. Screening conducted at 12 activated sites. Pre-screening candidates are not included.



Safety, CSF PGRN and serum NfL are the focus of this update

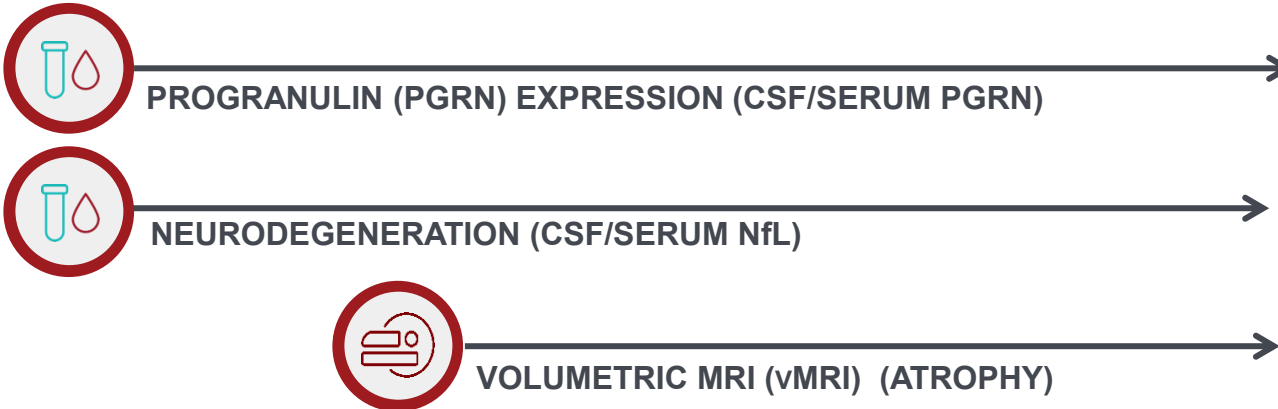


SAFETY



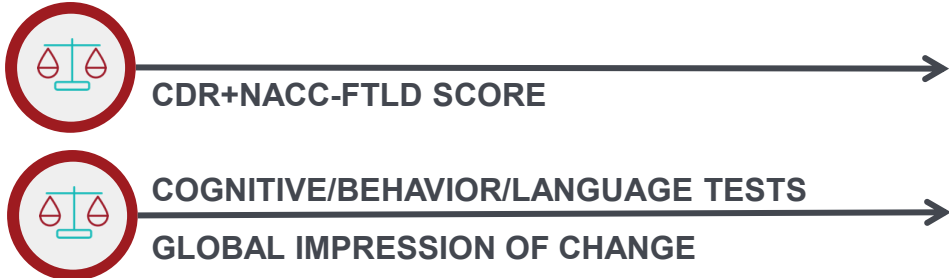


BIOMARKERS





CLINICAL SCALES

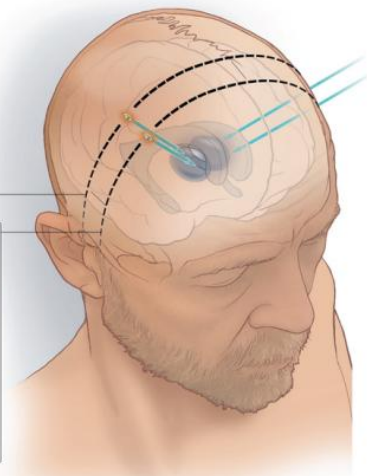
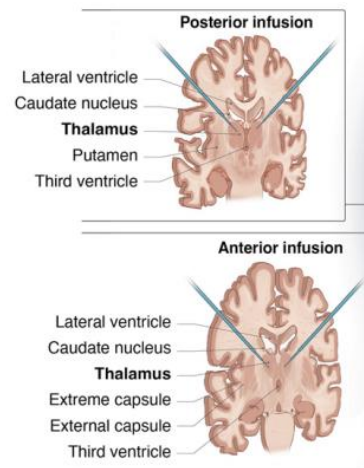


Baseline characteristics

Characteristic	All Cohorts
n	17
Age, years, mean (SD)	60.1 (8.8)
Sex, n	
Male	14
Female	3
Primary FTD phenotype, n	
bvFTD	9
PPA	8
Disease duration, years, mean (SD)	2.0 (1.9)
CDR plus NACC FTLD, mean (SD)	
Global Score	1.3 (0.6)
Sum of Boxes Score	6.8 (3.1)

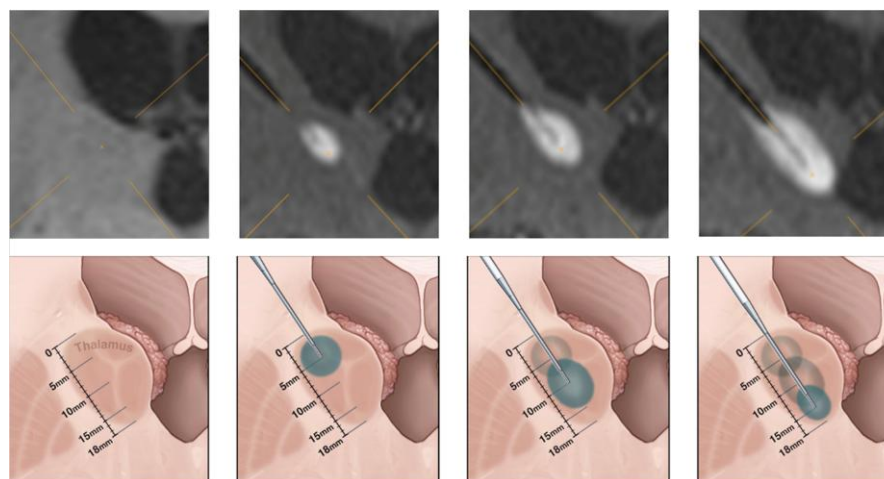


Standardized (protocolized) intrathalamic administration procedure implemented across 5 neurosurgical centers



Standardized procedure

Three-step procedure implemented on Participant #4 and carried forward.

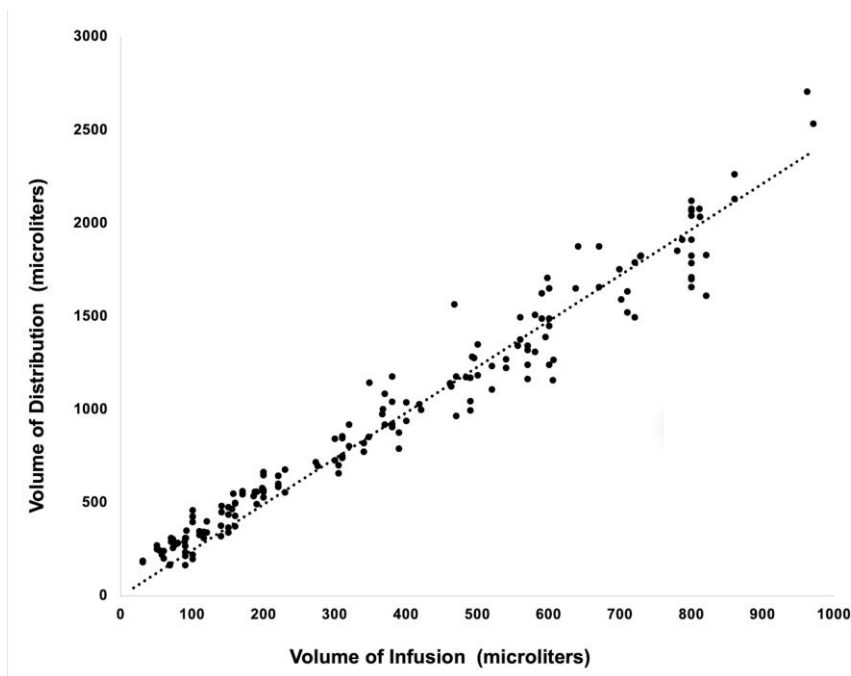


Initial insertion
Rate 1

Middle position
Rate 2

Final position
Rate 3

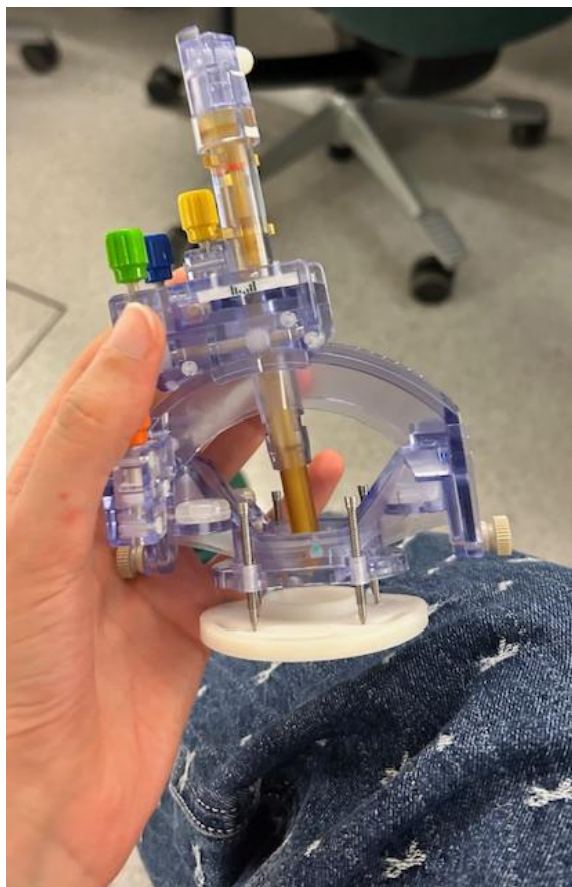
Convection Enhanced Delivery (CED) increases volume of distribution



Within infusion assessments of **volume of distribution** compared with **volume of infusion** show linearity of $V_d:V_i$ ratio throughout the infusions



Neurology-neurosurgery collaboration supporting AVB-101 administration



MRI compatible Smartframe XG™



Percutaneously mounted frames aligned to trajectories

Smartflow™ Neuroventricular Cannula



Prof. Hjalmar Bjartmarz adjusting cannulas
(Lund, SE)





MRI

Pre-Op

Entry

Mount

Target

Align

Adjust

Insert

NOT FOR CLINICAL USAGE
NEUROLOGICAL ORIENTATION

TOOLS



Fusion

AC-PC

Frame

Compare

Pre-Op

SIDE:

RIGHT

TRAJECTORY:

R Posterior

LAYOUT:

Oblique + Pointwise

Trajectory Orthogonal 1

HA

R

Trajectory Orthogonal 2

HR

PL

Trajectory Perpendicular

AF

RF

Anatomical Coronal

H

R

Anatomical Sagittal

H

P

Anatomical Axial

A

R

COLLAPSE



70% 30%



- Frame [7]
- Insert [25]
- Grid [1]
- Pre-Op [2]

AVB-101 and the administration procedure were generally safe and well-tolerated

Category	
AEs (all)	131
TEAEs (all)	115
Perioperative TEAEs	51
SAEs (all)	5
Related to AVB-101	0
Related to administration procedure	1

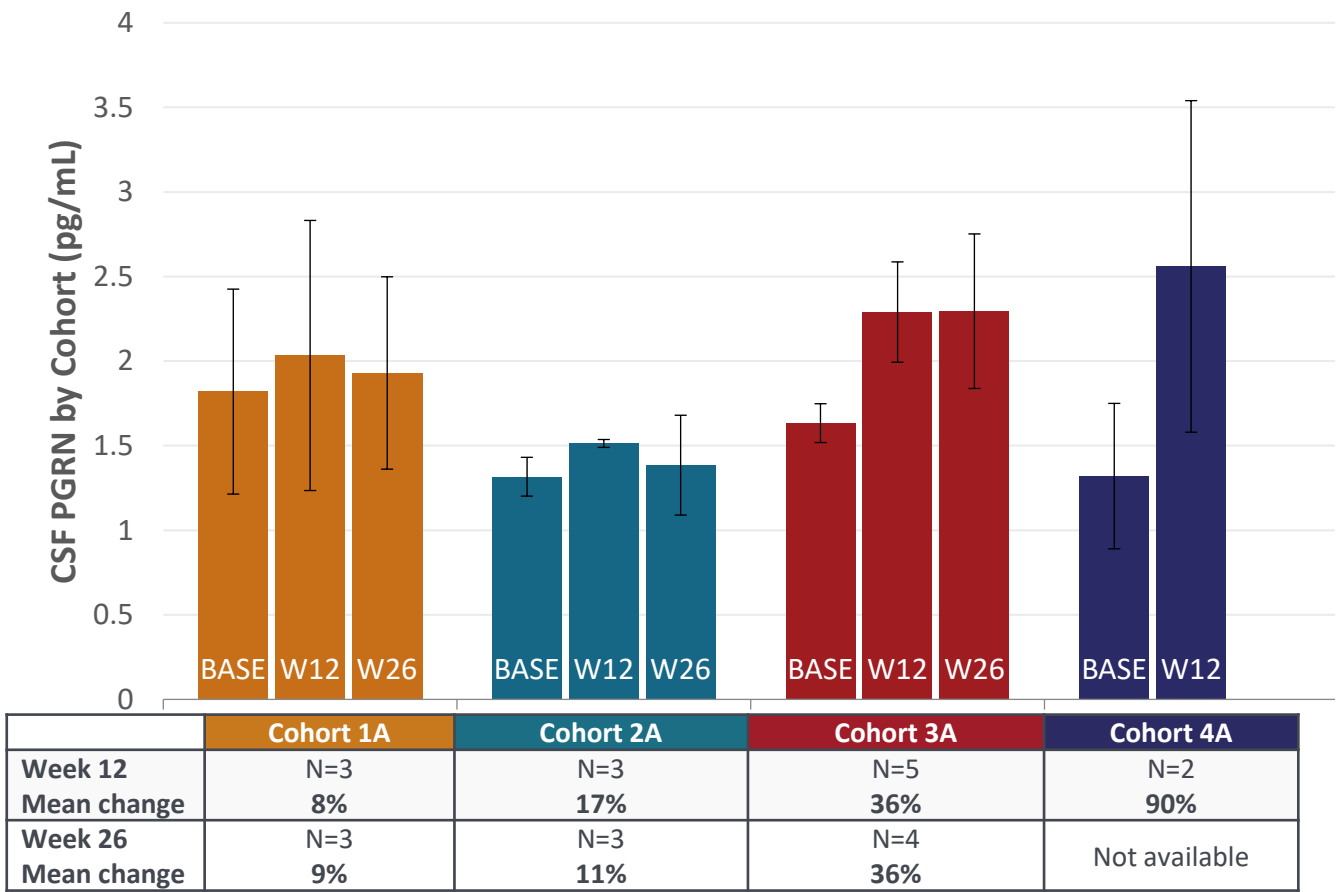
AE = adverse event; TEAE = treatment-emergent adverse event;
SAE = serious adverse event

- Follow-up ranges from 2 weeks post-dosing in the most recently dosed participant to more than 30 months in Cohort 1A
- Safety of intrathalamic delivery was consistent with prior intraparenchymal experience
- No SAEs related to AVB-101. No SUSARs.
- Five SAEs occurred in three participants:
 - One was assessed as a clinically silent imaging finding related to the administration procedure
 - The remaining four were *not* related to the administration procedure
- No prophylactic or reactive immunosuppression was required in any participant
- No dose-limiting toxicity observed to date

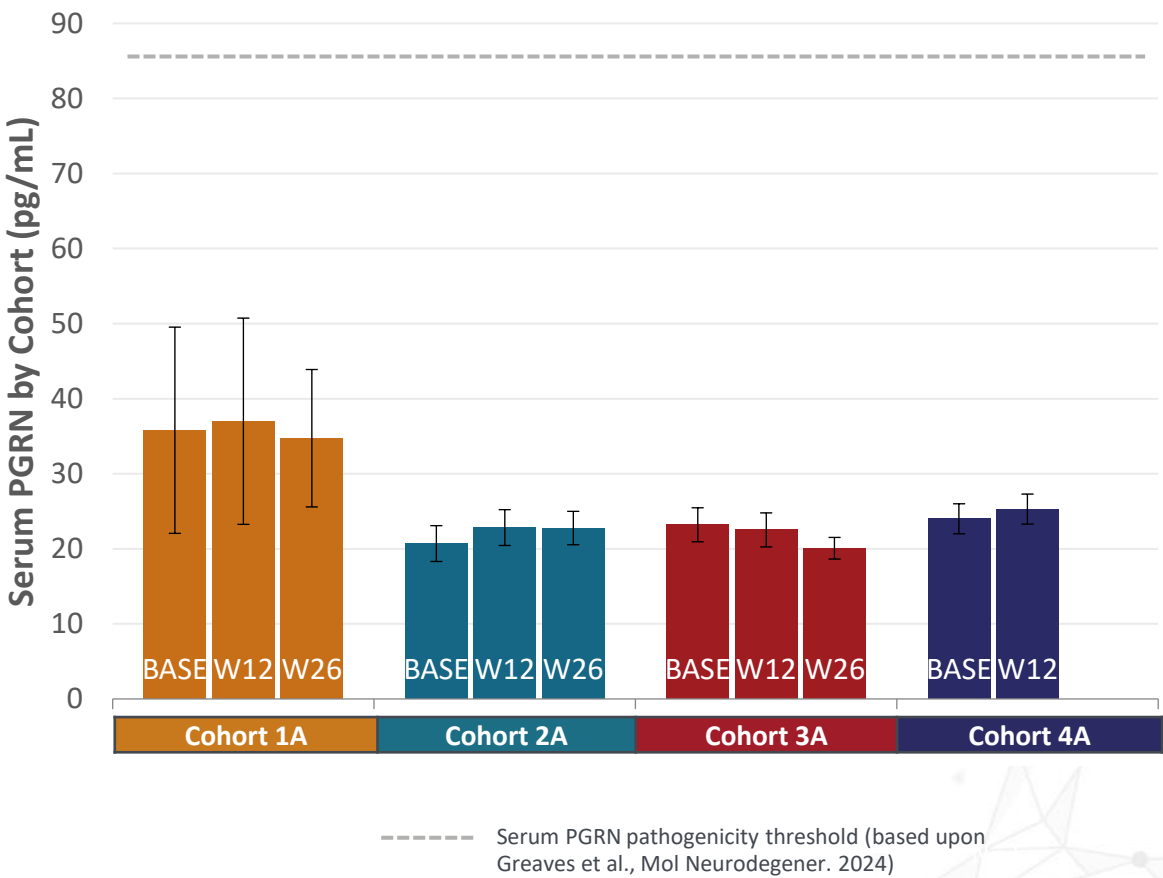


Early signs of dose-dependent CSF PGRN elevation confirms thalamic expression

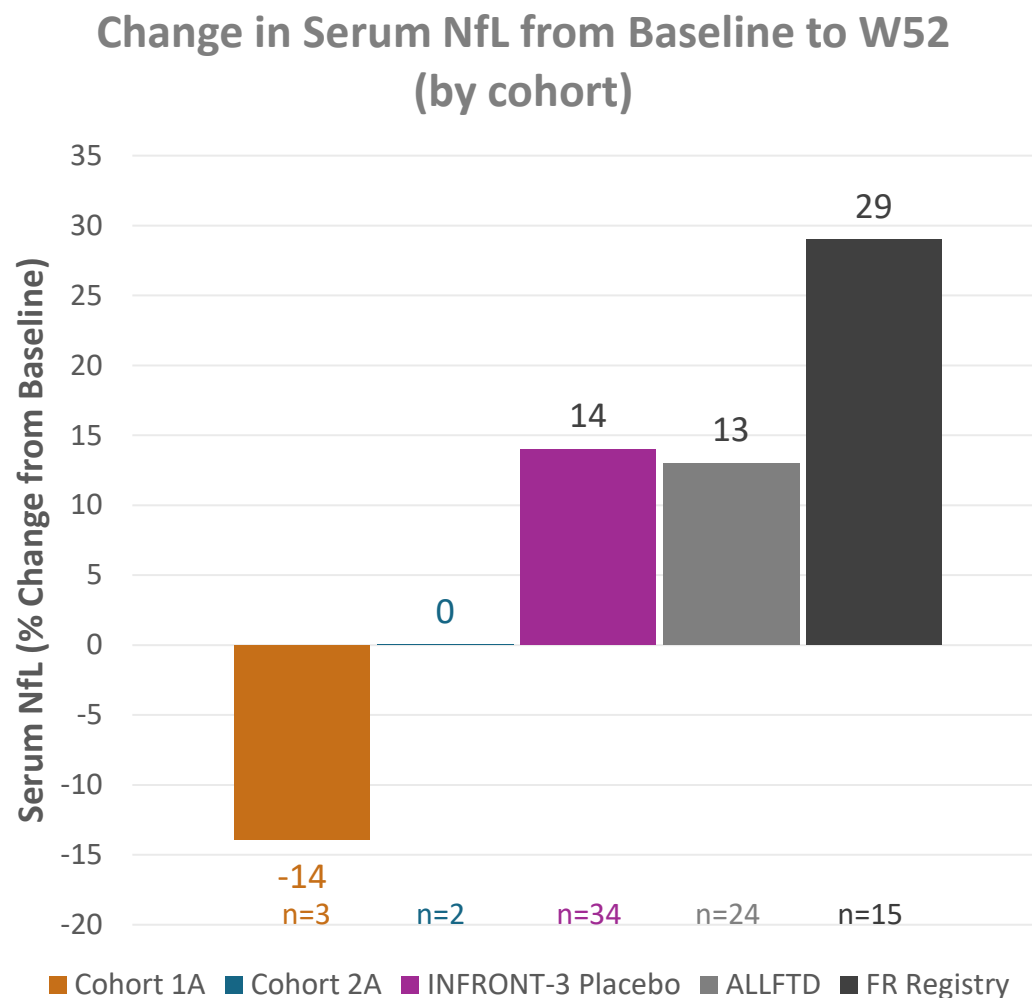
CSF PGRN (Baseline, Week 12, Week 26)



Serum PGRN (Baseline, Week 12, Week 26)



NfL could be a potential biomarker of disease modification



Preliminary comparison with observational studies and placebo data do not show increases in NfL expected with disease progression

Alector INFRONT-3 Placebo data (n=34). AAN Meeting, 21 April 2026
ALLFTD (n=24): AviadoBio analysis of ALLFTD natural history cohort
French Research Network FTD cohort (n=15): Saracino D, et al. *J Neurol Neurosurg Psych* 2021; 92:1278-1288



Summary

- **17 participants** have been dosed across **four ascending dose cohorts**
 - Recruitment and dosing in Cohort 4 are ongoing
- MRI-guided, convection-enhanced intrathalamic administration was **consistent across participants and 5 neurosurgical centers**, with a stable Vd:Vi relationship
- AVB-101 and its administration procedure has been generally safe and well-tolerated
 - **No SAEs related to AVB-101**; no dose-limiting toxicity
- **Dose-dependent increase in CSF PGRN** with unchanged serum PGRN, consistent with neuron-restricted expression
- Potentially interesting longer term trends in NfL at/below baseline in lowest dose cohorts
- Data from this study will inform **dose selection and future studies** of AVB-101



Acknowledgements

We thank the Patients and caregivers, our investigators, and our collaborators

